REMARKS

I. CLAIMS AMENDMENTS

The Applicants have amended claims 55 and 70 to indicate that the liposomes consist essentially of "empty aqueous interiors". The addition of language "consisting essentially of" means that the aqueous interiors are free of drug but does not mean that the aqueous interiors are free of non-drug materials such as water and other inert molecules.

The amended claims are fully supported by the specification and do not constitute new matter. Specifically, the recitation of "consisting essentially of empty aqueous interiors" in Claims 55 and 70 is supported by the specification at p. 7, *ll.* 25-31 and 37 to p. 8, *l.* 1.

Claims 57-59 and 72-74 have been amended to indicate the therapeutically effective amount of liposomes in a pharmaceutical composition of Claim 55 or 70 used to treat an average person of 70 kg of weight. Support for these amendments can be found at p. 15, *ll.* 11-13 of the specification.

II. REJECTION UNDER 35 U.S.C. § 112

Claims 55-84 stand rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Office is of the opinion that the terms "empty aqueous cores" and "Gaussian distribution" in Claims 55 and 70 have no support in the specification and therefore, deemed to be new matter. Applicants respectfully traverse the rejection.

With respect to the term "empty aqueous cores", the rejection is moot in view of the amendments to Claims 55 and 70 presented in the instant reply.

With respect to the term "Gaussian distribution", we refer to the instant specification. The specification describes the preparation and use of a population of liposomes having a mean diameter of 125 nm plus or minus 30 nm wherein at least 68% of the liposomes have such diameter, as measured by QELS (Quasi-Electric-Light-Scattering) analysis, utilizing a Nicomp Model 370 submicron laser particle sizer equipped with a 5-mW He-Ne Laser (*see* specification on p. 17, *ll.* 8-23). As explained in the specification, the Nicomp QELS system used to characterize the liposome population analyzes fluctuations in light-scattering intensities due to vesicle diffusion in solution. *Id.* The measured diffusion coefficient is used to obtain the average hydrodynamic radius and the mean diameter of liposomes is expressed as the mean plus or minus 1 standard deviation (125 ± 30 nm) (*see* specification at p. 17, *ll.* 8-23), arrived at using a Gaussian analysis (see, The *Nicomp Model*

370 Submicron Laser Particle Sizer User Manual at pp. 24-25, entitled "*The Simplest Approach to Size Distributions: Gaussian Analysis*", of record).

This analysis uses well-known and accepted mathematical principles to characterize the size distribution of a population, which is expressed as a Gaussian distribution, also known as a "normal" or "bell-shaped" distribution (*see An Introduction to Statistics-Lesson 6: The Bell Shaped, Normal Gaussian Distribution*, of record). In a Gaussian distribution 68% of the data elements are within one standard deviation of the mean, 95% are within two standard deviations, and 99.7% are within three standard deviations. (*Id.* at p. 2, "The Empirical Rule").

Thus, Applicants respectfully submit that the specification on p. 17, *ll.* 8-23 supports the term "Gaussian distribution" and therefore, respectfully request that the rejection be withdrawn.

III. DOUBLE PATENTING REJECTION

Claims 55-84 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-6 of U.S. Patent No. 6,139,871.

Applicants submit herewith a Terminal Disclaimer in connection to U.S. Patent No. 6,139,871. Thus, the rejection is moot.

IV. REJECTION UNDER 35 U.S.C. § 103 OVER HAGER *ET AL.*

Claims 55-84 stand rejected under 35 U.S.C. 103(a) allegedly as being unpatentable over Hager *et al.* (EP 0470437). The Office is of the opinion that it would have been obvious to an artisan of ordinary skill to use liposomes for the treatment of atherosclerosis based on the teachings of the reference. Applicants respectfully traverse the rejection.

A finding of obviousness requires that the prior art both suggest the invention and provide one of ordinary skill with a reasonable expectation of success. *In re O'Farrell* 853 F2d 894, 903, 7 USPQ2d 1673 (Fed. Cir. 1988). Secondary considerations such as unexpected results must be considered if present. *Stratoflex, Inc. v. Aeroquip Cor*p., 713 F.2d 1530, 1538-39, 218 USPQ 871, 879 (Fed. Cir. 1983); *In re Merck & Co., Inc.*, 800 F.2d 1091, 1096, 231 USPQ 375, 378 (Fed. Cir. 1986). Here, the Applicant's pharmaceutical composition comprising liposome populations having the claimed Gaussian distribution is not suggested by the prior art and achieves unexpected results.

Applicant's unexpected results lie in the discovery that liposomes having the claimed size distribution wherein at least 68% of the liposomes have a mean diameter of 125 ± 30 nm: (1) do not substantially raise LDL or esterified cholesterol levels; and (2) mobilize more cholesterol from peripheral tissues (such as atherosclerotic plaques) than an

equivalent amount (per weight) of liposomes having a different Gaussian distribution with smaller liposomes (*see* Example 1). Liposomes with a size distribution having a smaller mean diameter can cause a substantial rise in LDL or esterified cholesterol levels (bad cholesterol) which is associated with the development and progression of atherosclerosis, thereby destroying the usefulness of the liposomes for clinical use. (*See*, Rodrigueza *et al.* 17 Arterioscler. Thromb. Vasc. Biol (10): 2132-2139 (1997)). Rodrigueza *et al.* states that large unilamellar liposomes (123 ± 35 nm) were more efficient in mobilizing unesterified cholesterol than small unilamellar liposomes (34 ± 30 nm), and animals treated with small unilamellar liposomes developed elevated concentrations of esterified cholesterol in contrast to animals treated with liposomes greater than about 123 ± 35 nm which showed no change in esterified cholesterol levels.

Prior to the present invention, only small liposomes (*e.g.*, 21-60 nm) were thought to be useful for the treatment of atherosclerosis. For example, it was generally assumed that the smaller the liposome size, the greater the circulation half-life, and therefore the more cholesterol mobilized (Gregoriadis and Senior, Life Sci. 113:183-192 (1986)). It was also expected that smaller liposomes would produce a greater number of HDL-like particles, thus promoting efflux of sterol from peripheral tissues (*see* p. 5, *ll.* 15-28 of the specification citing several prior publications related to this subject). Accordingly, the view prior to the present invention was that small liposomes (*i.e.*, 21-60 nm) were better than larger ones (*i.e.* 123 ± 35 nm). This is a clear teaching away from the claimed invention which contradicts any contention of obviousness.

Hager *et al.* teaches liposomes having mean diameter of 50-180 nm (*see* col. 2, line 26 and col. 3 line 57) and provides specific examples of 75 nm (*see* Examples 1, 4 and 6), 60 nm (*see* Example 2), and 58 nm (*see* Example 7).[1] Thus, the reference, considered as a whole, focuses on mean liposome diameters much lower than that claimed. Clearly, Hager *et al.* focuses away from a specific mean diameter range of 123 ± 35 nm as claimed in the instant invention. As a result, Hager *et al.* does not render the claims obvious.

Further, Applicants respectfully submit that the Office has failed to establish a case of *prima facie* obviousness with respect to Hager *et al.* It is improper to shift the burden to the applicant before the Office established a proper case of *prima facie* obviousness.

The Examiner argues that Applicants must prove that Hager *et al.* does not teach the Gaussian distribution (*see* p.5 of the Office Action). First, Applicants respectfully disagree. When claims are rejected under 35 U.S.C. § 103(a), the Office bears the burden of establishing *a prima facie* case of obviousness. *In re Bell*, 26 USPQ2d 1529, 1531 (Fed. Cir.

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[1] Hager *et al.* also has an example of 129 nm liposomes loaded with a DNA-marker (Example 3). This example does not relate to a blank liposome in that it contains a DNA-marker, as discussed on page 9 of the instant response.

1993). Therefore, the burden is clearly on the Examiner to prove that Hager *et al.* does teach the claimed Gaussian distribution. Second, if the Examiner is arguing that Hager *et al.* inherently discloses the claimed Gaussian distribution, Applicants respectfully disagree. More importantly, such is irrelevant as the Gaussian distribution for the alleged teaching in Hager *et al.* of 129 nm liposome would be, if disclosed, distinct from that claimed herein.[2] Indeed, the percentage of liposomes at or below 125 nm in Hager's composition would be distinct from that claimed herein. Significantly, the Hager's liposomes of 129 nm contain a DNA marker thus putting them outside the scope of the present claims. Contrary to the Examiner's rejection, Hager *et al.* exemplifies only blank liposomes of much lower sizes: 58 nm, 60 nm and 75 nm. Thus, when read as a whole, as is legally required (*In re Gore*, 220 USPQ 303 (Fed. Cir. 1983)), the skilled artisan would be taught that blank liposomes of Hager *et al.* must be smaller. Alternatively, the skilled artisan would be taught that the broader range of 50-180 nm would be useful. Such teachings which equate small liposomes with larger ones are directly contrary to the claimed composition.

In sum, Hager *et al.* does not teach or suggest liposome populations having the claimed mean diameter or Gaussian distribution thereof. Thus, the claimed invention is not obvious over the cited reference, and it is respectfully requested that the rejection be withdrawn.

V. REJECTION UNDER 35 U.S.C. § 103 OVER WILLIAMS IN COMBINATION WITH HAGER *ET AL.*

Claims 55-84 stand rejected under 35 U.S.C. 103(a) allegedly as being unpatentable over Williams (BBA, 875:183-194, (1986)) in combination with Hager *et al.* (EP 0470437). The Office alleges that one of ordinary skill in the art would be motivated to use liposomes larger than 50 nm described in Williams with a reasonable expectation of success based on the teachings of Hager *et al.* Applicants respectfully traverse the rejection.

Williams alone or in combination with Hager *et al.* does not suggest the invention since Williams does not suggest using a population of liposomes falling within the claimed Gaussian distribution. Indeed, Williams *teaches away* from the claimed invention since he describes the preparation of SUVs[3] and the uptake of endogenous cholesterol using SUVs administered to dogs. Thus, Williams discloses liposomes that are smaller than those

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[2] Applicants do not concede that Hager *et al.* discloses or enables such a composition.

[3] In Williams 1986, the phospholipid dispersion was prepared using ultrasonic irradiation (with a titanium probe) for a total of 40 minutes, followed by ultracentrifugation for 1 hour at 100,000 x g to remove fragments of titanium shed by the sonicator probe (*see* Williams 1986 at p. 184, col. 2, last paragraph). This method results in the production of SUVs - a result confirmed by the data in Williams 1986, Fig. 5 which shows that Williams' SUVs co-elute with the LDL fraction ("P1"), which is known to be 30 nm.

presently claimed. In combination with teachings of Hager *et al.* who advocates small blank liposomes (mean diameter 58-75 nm) (*see* examples 1, 2 and 4-6) as better choice to treat atherosclerosis, the two references in fact *teach away* from the pharmaceutical composition for the treatment of a vascular disease comprising unilamellar phospholipid liposomes having a mean diameter of about 125 ± 30 nm as claimed. Hence, Williams alone or in combination with Hager *et al.* does not render Claims 55-84 obvious.

In sum, the claimed invention recites a narrower population of liposomes neither taught nor suggested by the cited art. Accordingly, it is respectfully requested that the rejection be withdrawn.

Applicants also point out that any incentive to combine these references would be based upon their common disclosure of small blank liposomes again teaching away from that claimed.

VI. REJECTION UNDER 35 U.S.C. § 103 OVER WILLIAMS IN VIEW OF LIU

Claims 55-84 stand rejected under 35 U.S.C. 103(a) allegedly as being unpatentable over Williams (1984 or 1986) in view of Liu. The Office alleges that to prepare liposomes of Williams (1984 or 1986) having sizes within the claimed range would have been obvious to one of ordinary skill in the art since liposomes of those sizes are able to survive the circulation system for longer periods as taught by Liu. Applicants respectfully traverse the rejection.

Williams (1984) teaches liposomes corresponding to small unilamellar vesicles (SUVs) with mean diameter of about 21-50 nm and 30-60 nm (p. 419, lines 22-23; p.422, lines 43-45). Similarly, Williams 1986 describes the preparation of SUVs and the uptake of endogenous cholesterol when the SUVs are administered to dogs (*see* discussion in section V above).

The Liu paper reports on a study designed to develop liposomes that are both acid sensitive and have a prolonged half life. Liu begins research from the premise that small liposomes are pH-sensitive (*see* col. 2, page 348) and that large unilamellar liposomes are not stable in serum (Id.) Liu also teaches that smaller liposomes are better as they have longer circulation time than large liposomes, which is consistent with Gregoriadis (1986) discussed in Section IV above. Thus, Liu does not remedy the deficiencies of Williams. Nor does Liu teach the use of larger liposomes than in Williams. More important, Liu teaches the use of liposomes with ganglioside GM[4] to impact upon biodistribution and circulation time and thus is not relevant to the claimed empty liposomes. In sum, Liu does not teach or suggest the

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[4] Gangliosides have therapeutic effects (*See, e.g.*, Merck Index, 12th Ed. Monograph, 4379; Medical Breakthroughs - Learn More About Heart Diseases, Definition of GM-1 Ganglioside at http://www.healthcentral.com/bcp/main printed on December 9, 2004) and were used by Liu to modify the biology of the liposomes.

claimed composition having liposomes of such mean diameter much less with the claimed Guassian distribution, and Liu can be said to be outside the claim scope as it is not blank liposomes as claimed.

Although there is no motivation to combine the teachings of Williams (1984 or 1986) with the teachings of Liu, if combined, the combination clearly teaches small liposomes, *i.e.* teaches away from the invention as claimed. There is no disclosure in Liu of blank liposomes of the proper size nor a suggestion of pharmaceutically acceptable liposomes of a size larger than in Williams.

Additionally, Williams teaches a significant increase in LDL or esterified cholesterol levels in four hours after SUVs infusion (*see* Williams 1986, Fig. 2A, the peak labeled "P1" [LDL] at four hors ["t = 4h"]). The Office argues that the examination of the mentioned data in Williams did not reveal a statistically significant difference between values for the controls and the liposomes. Applicants respectfully disagree and submit that the experimental data in Williams corresponding to Fig. 2A, t = 4h, the peak labeled "P1" shows a dramatic (and surely statistically different) increase in the LDL levels. Thus, Williams 1986 not only discloses liposomes that are smaller than those that presently claimed but also teaches liposomes that cause an increase in LDL level after administration. As such, the reference teaches away from the present invention claiming that the liposomes are effective in promoting cholesterol efflux without causing a substantial increase in LDL or esterified cholesterol levels. Accordingly, Williams (1984 or 1986) in view of Liu does not render the instant claims obvious. Therefore, it is respectfully requested that the rejection be withdrawn.

CONCLUSION

Entry of the foregoing amendments and remarks is respectfully requested. No other fee than the extension of time fee is believed to be due with this Reply. However, if any other fee is required, please charge the fee to Deposit Account No. 503013. In view of the above remarks and amendments, it is submitted that the presently pending claims are in form for allowance and early action to that end is requested. If any issues remain, the Examiner is requested to telephone the undersigned at (858) 314-1130.

Respectfully submitted,

Date: December 22, 2004

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